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**Modulation of soleus H-reflexes and somatosensory conditioning  
induced by position and rhythmic cycling of the arms**

by



Alain Frigon

A thesis submitted to the Faculty of Graduate Studies and Research in partial  
fulfillment of the requirements for the degree of Master of Science.

Faculty of Physical Education and Recreation

Edmonton, Alberta

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**University of Alberta**

**Faculty of Graduate Studies and Research**

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled “Modulation of soleus H-reflexes and somatosensory conditioning induced by position and rhythmic cycling of the arms” submitted by Alain Frigon in partial fulfillment of the requirements for the degree of Master of Science.





## **Abstract**

The present study investigated the effects of position and cycling of the arms on reflex excitability in the legs. Soleus H-reflexes were recorded with the subjects holding their arms stationary at two positions or while performing arm cycling using a custom-made ergometer. Two different somatosensory conditioning methods designed to decrease (sural nerve) or increase (common peroneal nerve) presynaptic inhibition at Ia afferent terminals of the soleus were used to determine the locus of modulation. Arm cycling significantly reduced the amplitude of soleus H-reflexes compared to stationary controls. Additionally, arm position and movement influenced conditioning volleys from sural and common peroneal nerves onto the soleus H-reflex pathway. The results suggest that interlimb pathways coupling the cervical and lumbosacral spinal cord are active during movement and that they might be involved in coordinating the arms and legs during movement.





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## CHAPTER 1 – Introduction and review of literature

### *Introduction*

Coordination of the fore- and hindlimbs (interlimb coordination) is a well-established feature of quadrupedal locomotion. In humans, rhythmic activities such as walking, running, and swimming require the coordinated movement of our upper and lower limbs. Furthermore, crawling, a quadrupedal form of human locomotion is present during infancy. Interlimb coordination is thought to stem from neural linkages connecting cervical and lumbosacral networks in the spinal cord. Several studies have identified neural connections between the arms and legs by stimulating nerves in the periphery. These responses are termed “interlimb reflexes”, and they occur at pre-volitional latencies in either the arms or legs as a result of perturbations (muscle stretch, nerve stimulation, etc.) of the lower or upper limb, respectively. Interlimb reflexes have been extensively studied in animals and have recently received attention for the control of human bipedal locomotion (reviewed in Dietz 2002). It has been well established that during movement, reflexes in the arms and legs, evoked by stimulating nerves in the same limb, are modulated according to behavioral context (task-dependence) and specific phases of a motor task (phase-dependence). However it is presently unclear how postural modifications or movement of the arms and legs can influence interlimb pathways.

Although the focus of this review is on human studies much of the groundwork comes from data recorded in other animals. For quadrupedal locomotion, a coordinated movement of the fore- and hindlimbs is of prime importance. In cats, stretch and cutaneous reflexes in forelimb muscles are strongly modulated by stimulation of hindlimb nerves (Miller et al. 1973). Similarly, stimulation of forelimb nerves strongly influences the excitability of hindlimb motoneurons (Schomburg et al. 1978). Interlimb pathways innervating extensors and flexors are reciprocally organized (Miller et al. 1973). These findings suggest that interlimb coordination of the fore- and hindlimbs is highly organized in cats.





In humans, short latency (< 45 ms) interlimb responses observed in several studies indicate a spinal reflex pathway (Calancie et al. 1991, 1996, 2002; Meinck and Piesiur-Strehlow 1981; Piesiur-Strehlow and Meinck 1980; Zehr et al. 2001a). Additionally, Calancie and colleagues (1991, 1996 and 2002) provide convincing evidence that interlimb responses are spinal reflexes. Interlimb responses were clearly recorded in spinal cord injured subjects suggesting a direct propriospinal pathway between the arms and legs. Studying interlimb responses is important in demonstrating wide-ranging neural interconnectivity between the arms and legs and how they might be important in controlling human movement.

It has been proposed that interlimb coordination of upper and lower limbs involves coupling between cervical and lumbosacral enlargements in the spinal cord through long propriospinal neurons (Delwaide et al. 1973, 1977; Dietz et al. 2001; Dietz 2002; Eke-Okoro 1994; Meinck and Piesiur-Strehlow 1981; Miller et al. 1973; Miller et al. 1998; Skinner et al. 1980; Zehr et al. 2001a). These propriospinal networks have been found in several species, including man (Nathan et al. 1996), and are thought to mediate large changes in reflex excitability (Miller et al. 1973).

This chapter reviews the evidence for a spinal pathway in man coupling the cervical and lumbosacral enlargements of the spinal cord. The following sections address in turn: coordination of the arms and legs during locomotor tasks, anatomical studies revealing the presence of propriospinal interlimb pathways, interlimb pathway modulation of reflexes (stretch, cutaneous, and H-reflexes), mechanisms of reflex modulation, functional significance of interlimb connections, and a proposed organization of the system controlling human locomotion.

### ***Coordination of arms and legs***

During locomotor tasks that involve coordination of the arms and legs the frequency relationship of the two pairs of limbs remains locked over a range of movement velocities (Wannier et al. 2001). Detailed biomechanical analyses of locomotor activities reveal that the arms follow a specific movement pattern and



that there is active muscular contraction of the arms to produce movement. Arm movement does not arise purely because of mechanical interactions yielding a pendular motion (Jackson et al. 1983a, 1983b). Although human locomotion, such as walking, can easily be performed without any movement of the arms, the arm musculature contracts normally with the arms restrained (Fernandez-Ballesteros et al. 1965). Movement of the upper limbs during locomotion might have been conserved due to the existence of central pattern generators (CPG) and/or to produce a smooth coordinated locomotion (Jackson et al. 1983b). Not only do the arms and legs follow a similar pattern of muscular contraction during locomotor tasks but reflexes in the upper and lower limbs during rhythmic movements are also modulated similarly (Zehr and Kido 2001, Zehr et al. 2003, Zehr and Haridas 2003). The similarity in the pattern of reflex modulation of the arm and leg musculature indicates a similar organization of neural circuits at the cervical and lumbosacral levels of the spinal cord (e.g. CPGs). Movement of a limb has profound effects on reflex excitability of that same limb (reviewed in Brooke et al. 1997; Zehr and Stein 1999a) but also on that of the homologous contralateral limb (Collins et al. 1993). Thus neural circuits exist coupling homologous limbs during movement. What remains unclear is how movement can influence interlimb pathways interconnecting the arms and legs and how they might be important in controlling movements involving all four limbs.

### ***Propriospinal projections coupling cervical and lumbosacral networks***

In quadrupeds, neuronal coupling of fore- and hindlimbs is an important aspect of over-ground locomotion. For humans, the question remains, is this coupling vestigial or does it still have important functional implications for the control of movement? The next few sections present anatomical evidence of propriospinal neurons (spinal neurons traversing several segments and terminating within the spinal cord) in the cat, in the monkey, and in man coupling the cervical and lumbosacral segments of the spinal cord. The following sections begin to address the functional relevance of such pathways in man.





A vast network of propriospinal circuits coupling the cervical and lumbosacral segments has been documented in cats (Alstermark et al. 1987; Barilari and Kuypers 1969; Krutki et al. 1998; Matsushita et al. 1979; Miller et al. 1973; Molenaar and Kuypers 1978; Skinner et al. 1979; Yezierski et al. 1980). There are very precise and specific projections of propriospinal neurons in the spinal cord (Yezierski et al. 1980). Extensive coupling of various segments of the cat spinal cord have been identified using the retrograde transport of horseradish peroxidase (HRP) at levels of C1, T1, T6, L1, and L6 (Molenaar and Kuypers, 1978). A similar study identified cells at every level of the spinal cord which receive projections from L3 to S3 segments (Yezierski et al. 1980). Normally connections are far more extensive between segments in close proximity by way of short propriospinal neurons, but connections to distant segments also arise from long propriospinal neurons (Matsushita et al. 1979; Molenaar and Kuypers, 1978; Yezierski et al. 1980). Krutki et al. (1998) found propriospinal neurons from C6 projecting to sacral segments (S1/S2) with collaterals branching to lumbar segments (L4). The existence of collaterals branching to segments of the lumbosacral enlargement raises the possibility that the descending information can be relayed to several motor centers controlling different hindlimb muscles (Krutki et al. 1998). Skinner et al. (1980) identified long descending propriospinal neurons coupling the cervical enlargement and L2 segment. The role of these propriospinal neurons has been ascribed to coordinating movement between the fore- and hindlimbs in cats (Miller et al. 1973).

A few studies have identified neuronal coupling of cervical and lumbosacral enlargements of the spinal cord in primates, including humans (Molenaar and Kuypers 1978; Nathan et al. 1996; Skinner et al. 1979). In monkeys the organization of the long descending propriospinal tract is similar to the cat, although the distribution of neurons differs (Skinner et al. 1979). Injection of HRP in rhesus monkeys identified several long propriospinal neurons projecting from C1 and C6 to L6 (Molenaar and Kuypers 1978). In the human spinal cord, caudal to the cervical enlargement, reticulospinal fibres are progressively replaced by propriospinal fibres but some still descend to the lowest



sacral segments (Nathan et al. 1996). Similar to other species, anatomical data reveals that the majority of propriospinal fibres in humans from the thoracic, lumbar and sacral segments of the spinal cord are short (one to two segments long) but there are long propriospinal neurons coupling cervical and lumbosacral enlargements (Nathan et al. 1996).

The presence of these propriospinal connections between the cervical and lumbosacral enlargements suggests that they might be functionally important in the control of interlimb coordination (Skinner et al. 1980). Propriospinal pathways are similarly organized in different species (Menetrey et al. 1985) and have been conserved in humans (Nathan et al. 1996). Long descending propriospinal neurons are ideally located to convey sensory information between the upper and lower limbs and to coordinate motor functions between the arms and legs (Skinner et al. 1979). Other pathways that could possibly mediate interlimb responses will be addressed later.

### ***Earliest evidence of interlimb reflexes in humans***

Sherrington and Laslett (1903) first demonstrated interconnections between the cervical and lumbar spinal cord in the dog. Since then several studies have reported widespread neural interconnections between fore- and hindlimbs in cats (Miller et al. 1973; Schomburg et al. 1978). Up until a few decades ago no similar work had been performed in humans. Gassel and Ott (1973) observed responses in triceps surae following cutaneous stimulation of the shoulder, upper arm and foot. Kearney and Chan (1979) demonstrated responses in human arm muscles following noxious stimuli to the sole of the foot or ankle displacement (1981). The direction of ankle displacement also determined the nature of the response. Piesiur-Strehlow and Meinck (1980) stimulated the ulnar nerve at the elbow and evoked responses in several muscles of the leg. In a subsequent experiment stimulation of the radial, median, and ulnar nerves produced responses in several contracting leg muscles (Meinck and Piesiur-Strehlow 1981). Although these studies proposed that there was a neural linkage between the upper and lower limbs the first direct evidence of interlimb reflexes in humans came from



the work of Sarica and Ertekin in 1985. They recorded lumbosacral potentials using intrathecal recordings following stimulation of the median nerve at the elbow. They concluded that the potentials were conducted through fast conducting propriospinal pathways and that they might be important in the coordination of movements and posture.

The next two sections will present the current body of knowledge supporting a neuronal linkage of cervical and lumbosacral regions of the spinal cord in humans. Modulation of stretch and H-reflexes by interlimb pathways will be addressed first followed by cutaneous reflexes.

### ***Interlimb pathway effects on stretch and H-reflexes***

This section reviews the electrophysiological evidence of a spinal pathway coupling the cervical and lumbosacral segments in the human spinal cord. Specifically, by examining the effects of nerve stimulation and postural modifications of the upper and lower limbs on the excitability of stretch and H-reflexes in the legs and arms, respectively.

Hoffmann (1918) first described the H-reflex. Electrical stimulation of the posterior tibial nerve, in the popliteal fossa, resulted in a short latency direct response (M-wave) and a longer latency reflex response (H-reflex) in the soleus (reviewed in Misiaszek 2003; Schieppati 1987). This technique is now used extensively as a means of assessing the integrity of the spinal reflex pathway in health and disease (Misiaszek 2003; Schieppati 1987). The amplitude of the H-reflex is strongly modulated between different tasks (task-dependency) and during different phases of a movement (phase-dependency) (reviewed in Brooke et al. 1997; Schieppati 1987; Zehr and Stein 1999a; Zehr 2002). Although stretch and H-reflexes are not identical they depend to a large extent on the synaptic connection between group Ia muscle afferents and alpha-motoneurons (Capaday and Stein 1986).

The presence of interlimb pathways has been demonstrated by stimulating peripheral nerves in the arms and legs and recording changes in the excitability of stretch and H-reflexes. Gassel and Ott (1973) observed changes in soleus H-





reflex excitability following cutaneous stimulation of the ipsilateral shoulder and upper arm, with latencies ranging from 20-150 ms. Delwaide and Crenna (1984) noted that stimulating cutaneous branches of the median nerve innervating digits of the hand facilitated soleus H-reflexes. They also found a biphasic facilitation of stretch reflexes in the biceps and triceps brachii following stimulation of the sural nerve at the ankle. The first peak of facilitation occurred 35-45 ms after sural nerve stimulation, which would exclude supraspinal influences.

Furthermore, soleus H-reflexes were facilitated by stimulating the ulnar nerve (Meinck and Piesiur-Strehlow 1981) and the median nerve (Kagamihara et al. 2003) at the elbow. Kagamihara et al. (2003) attributed this facilitation to reducing presynaptic inhibition at the Ia afferent terminal of the soleus through a long-loop pathway reaching levels at least as rostral as the pons.

Postural modifications of the upper limbs can be used to determine if connections project, either directly or transcortically, from receptors in the arms to lumbosacral segments of the human spinal cord. A few studies have examined the effects of passive arm positioning on the amplitude of stretch and H-reflexes in the lower limb (Delwaide et al. 1973, 1977; Eke-Okoro 1994). One general feature is that stretch and H-reflexes display similar patterns of modulation with different positions of the arms with the effects being more pronounced for stretch reflexes (Delwaide et al. 1973). Quadriceps and soleus stretch reflexes display similar patterns of modulation while the biceps femoris stretch reflex is different (Delwaide et al. 1977). In the right soleus and quadriceps, flexion at the shoulder joint, so that the right arm is positioned forward (45-90° in front of the mid-axillary line) results in facilitation of stretch (Delwaide et al. 1977) and H-reflexes (Delwaide et al. 1973; Eke-Okoro 1994). When the left arm is placed in the same position an inhibition occurs. When the right shoulder is extended (30° behind the mid-axillary line) reflexes in the right soleus are inhibited (Delwaide et al. 1973, 1977; Eke-Okoro 1994). The effects are larger when two facilitory or inhibitory maneuvers, such as shoulder flexion of the right arm and shoulder extension of the left arm, are combined (Delwaide et al. 1977). In the case of biceps femoris stretch reflexes, opposite effects occur. Flexion of the right



shoulder (60° in front of the mid-axillary line) reduces the amplitude of biceps femoris stretch reflexes while extension of the same arm facilitates the reflexes (Delwaide et al. 1977). Furthermore, flexion of the left shoulder facilitates biceps femoris stretch reflexes in the right leg while shoulder extension is inhibitory (Delwaide et al. 1977). This suggests that upper limb position has differential effects on extensors and flexors of the lower limbs. Facilitation or inhibition of stretch reflexes is larger for the more proximal muscles (quadriceps and biceps femoris) when compared to the more distal soleus (Delwaide et al. 1977).

To date only a few studies have investigated the effects of upper limb movements on H-reflex excitability in muscles of the lower limb (Hiraoka and Nagata 1999; Hiraoka 2001; Kasai and Komiyama 1996; Kawanishi et al. 1999). Kasai and Komiyama (1996) examined soleus H-reflexes during ballistic contractions of the arm (rapid shoulder flexion) standing humans. Preceding the ballistic contraction and just after the onset of shoulder EMG, the soleus H-reflex was depressed and then facilitated, respectively (Kasai and Komiyama, 1996; Kawanishi et al. 1999). This period of depression corresponded with an increased activity of ipsilateral biceps femoris. They attributed their findings to projections onto soleus motoneurons from biceps femoris. Facilitation of the soleus H-reflex, which started approximately 50 ms following the onset of anterior deltoid activity, could be due to shoulder activity or displacement of the arm since previous studies have found that soleus stretch and H-reflexes are influenced by upper limb position (Delwaide et al. 1973, 1977; Eke-Okoro 1994).

In another study, passive flexion and extension of the elbow joint increased the amplitude of the soleus H-reflex in a velocity-dependent manner (Hiraoka and Nagata 1999). This facilitation was attributed to increased excitability of soleus motoneurons due to afferent discharge from the upper limbs. In contrast to passive movement, active arm movement reduced the amplitude of soleus H-reflexes (Hiraoka 2001). In that study soleus H-reflexes were evoked while subjects performed rhythmical arm swing in a seated position. A greater velocity of arm swing produced a greater reduction in soleus H-reflex amplitude (Hiraoka 2001). Ipsilateral swing of one arm and reciprocal arm swing



of both arms depressed soleus H-reflex but only when the ipsilateral arm was in shoulder extension behind the mid-axillary line (Hiraoka 2001). It was concluded that modulation of the soleus H-reflex is dependent on the phase of the upper limb. It is important to note that passive movement at the elbow joint facilitated soleus H-reflexes while active movement at the shoulder joint reduced soleus H-reflexes. Therefore movements (active or passive) at different joints can differentially influence soleus H-reflex excitability.

However, care should be taken in interpreting these findings. Both studies (Hiraoka and Nagata 1999; Hiraoka 2001) used H-reflexes as a percentage of  $H_{\max}$  (maximal H-reflex) (50% and 70%, respectively) as a measure of stimulus constancy. H-reflexes can show marked fluctuations in amplitude during a trial. Two very different intensities can elicit an H-reflex of the same size depending on which part of the M-H recruitment curve is being tested. For example an H-reflex at 70% Hmax can be evoked at low intensities on the ascending part of the curve and at a considerably higher stimulus intensity on the descending slope of the curve. This not only changes the strength of the afferent volley but reflexes from ascending and descending parts of the curve have been shown to display different sensitivity to modulation (Crone et al. 1990). It is unclear on which part of the curve these H-reflexes were evoked. Furthermore, subjects did not maintain the activation of the target muscle at a constant level. The level of activation of the motoneuronal pool significantly influences the amplitude of the H-reflex (Capaday and Stein 1987b). It is therefore difficult to ascertain if the modulation of the reflex is due to movement of the upper limbs or simply a change in the activation level of the soleus.

Changes in excitability of H-reflexes in the upper limbs with rhythmic oscillations (flexion-extension) of the foot have been investigated recently (Baldissera et al. 1998, 2002). The amplitude of flexor carpi radialis (FCR) H-reflexes changed according to the position of the ipsilateral foot with a peak facilitation occurring in the plantar flexed position and a dis-facilitation during dorsiflexion (Baldissera et al. 1998, 2002). Peak facilitation coincided with an EMG burst in the soleus. They concluded that the modulation was linked to





muscular activation of the foot movers and not to mechanical parameters of the movement. To assess the influence of descending pathways Baldissera et al. (2002) used transcranial magnetic stimulation (TMS) to facilitate FCR H-reflexes with short (2-3.5 ms) conditioning-test (C-T) intervals and inhibited reflexes with longer (40-60 ms) C-T intervals. The amplitude of TMS-facilitated H-reflexes was modulated similarly to the unconditioned reflexes during foot oscillations. At the longer C-T intervals the inhibited FCR H-reflexes did not modulate with foot oscillations. They concluded that corticospinal influences work in parallel with spinal mechanisms to modulate FCR H-reflexes during rhythmic oscillations of the ipsilateral foot (Baldissera et al. 2002).

These results suggest that postural modifications and nerve stimulation of the legs and arms can modulate stretch and H-reflexes of the upper and lower limbs, respectively. This provides evidence that connections between cervical and lumbosacral regions of the spinal cord exist and are influenced by movement and/ or postural modifications. However, due to the methodological concerns of previous studies raised in this section it is unclear what effect movement or position of the arms has on reflex excitability in the legs.

### ***Interlimb pathways and cutaneous reflexes***

Similar to H-reflexes, cutaneous reflexes are strongly modulated during movement (reviewed in Brooke et al. 1997; Zehr and Stein 1999a). Cutaneous reflexes in the arms and legs display nerve specificity; meaning that reflexes can vary in sign and amplitude according to the site of stimulation (Van Wezel 1997; Zehr et al. 1997, 1998, 2001b). Cutaneous reflexes in the lower limbs evoked by stimulating nerves in the ipsilateral foot exhibit task- and phase dependent modulation during walking (Van Wezel et al. 1997) and leg cycling (Zehr et al. 2001b). Similarly, cutaneous reflexes in the upper limbs following stimulation of nerves innervating the ipsilateral hand exhibit task- and phase-dependency (Zehr and Chua 2000; Zehr and Kido 2001; Zehr and Haridas 2003). Thus there are many similarities in reflex modulation in the upper and lower limbs (Zehr and



Kido 2001). Whether this neuronal coupling has been conserved between the cervical and lumbosacral spinal cord in humans will be addressed next.

Calancie and colleagues (1991, 1996, 2002) have reported interlimb responses in cervical spinal cord injured subjects. Electrical stimulation of mixed nerves in the leg led to reflex responses in muscles of both arms, particularly the intrinsic hand muscles. The ability to generate interlimb reflexes in spinal cord injured subjects and the relatively short latencies suggest that the interlimb reflex pathway does not require a supraspinal connection (Calancie et al. 1991, 2002). Calancie et al. (1991) were unable to evoke similar responses in able-bodied subjects. They attributed loss or interruption of tonic descending inhibition to explain why only spinal cord injured subjects displayed interlimb reflexes. However, previous (Delwaide and Crenna 1984; Gassel and Ott 1973; Kearney and Chan 1979) and recent (Kagamihara et al. 2003; Zehr et al. 2001a) demonstration of interlimb responses in neurologically intact subjects suggests that this is not the case. Stimulation of cutaneous nerves at the wrist (superficial radial nerve) and at the ankle (superficial peroneal nerve) elicited reflexes in contracting muscles of the arms and legs (Zehr et al. 2001a). Several reasons could explain why Calancie could not record interlimb reflexes in neurologically intact subjects (Zehr et al. 2001a). The different nerves studied in Zehr et al. 2001a and method of EMG recording are possible reasons. Another possibility is that Calancie studied neurologically intact subjects less extensively than spinal cord injured subjects since his description of methods and procedures were far less detailed (Zehr et al. 2001).

Interlimb cutaneous reflex pathways might be important in transmitting exteroceptive information for reflexive coordination of movement (Zehr et al. 2001a). Although a supraspinal modulation of interlimb reflexes is likely the early responses and the work done by Calancie and colleagues (1991, 1996, 2002) on spinal cord injured subjects would suggest a strong spinal component and propriospinal contribution to interlimb responses.



## ***Mechanisms of reflex modulation***

Since they appear to have different control mechanisms (Zehr et al. 2001b) this section will review separately mechanisms of reflex modulation for H-reflexes and cutaneous reflexes followed by a brief discussion on the possible neural mechanisms controlling interlimb coordination.

### **H-reflexes**

During movement, H-reflexes seem to be controlled by an interaction of peripheral and central factors (Zehr et al. 2001b). H-reflexes are strongly modulated by the level of activation of the motoneuron pool (Capaday and Stein 1987b; Verrier 1985; Zehr 2002). At fixed stimulus strength the amplitude of H-reflexes increases linearly as a function of the background EMG (Capaday and Stein, 1987b). Several studies have demonstrated this relationship (Capaday and Stein 1986; Capaday and Stein 1987a; Verrier 1985; Zehr et al. 2001b; Zehr et al. 2003). However, the amplitude of soleus H-reflexes progressively decreases from standing to walking to running despite large increases in soleus EMG (Capaday and Stein 1986, 1987a). Therefore the H-reflex is not strictly a function of EMG level during movement. However a stronger contraction (greater background EMG) will result in a larger H-reflex when comparing two identical movements (Zehr et al. 2001b, 2003).

Movement-induced modulation of H-reflexes is thought to be predominantly under the control of presynaptic inhibition (PSI) (Capaday and Stein 1986, 1987a, 1987b). It is thought that there is a tonic level of PSI, even at rest, and that it might vary between different muscles (Schieppati 1987). Inputs from multiple sources including feedback from other peripheral receptors (muscle spindles, Golgi tendon organs, cutaneous receptors) (Zehr 2002) could increase or decrease the level of PSI.

Methods have been designed to assess presynaptic control of H-reflexes. These methods condition H-reflexes by decreasing or increasing the level of PSI of Ia afferent terminals. Two methods of conditioning the soleus H-reflex are presented here: one decreases (sural nerve) and one increases (common peroneal nerve) PSI of the afferent pathway to soleus motoneurons.





Afferent feedback from the sural nerve, which innervates the lateral side of the foot, is thought to stabilise gait and aid in locomotion (Zehr et al. 1998). Hugon and Bathien (1967) first noticed that mild electrical stimulation of the sural nerve, below the lateral malleolus, facilitated the amplitude of soleus H-reflexes in the same leg. Several studies have since confirmed this result (Delwaide et al. 1981; Demaire et al. 1989; Demaire and Ciancia 2000; Honore et al. 1983; Lebizec et al. 1983). The facilitation peaks at a C-T interval of approximately 70-90 ms (Demaire and Ciancia 2000) and has been attributed to a reduction in PSI of Ia afferent terminals of soleus motoneurons (Demaire et al. 1989; Iles 1996).

The common peroneal nerve innervates ankle dorsiflexors and is thought to increase PSI to Ia afferents of soleus motoneurons (Capaday et al. 1995; Iles 1996; Zehr and Stein 1999b). The net effect is a decrease in the amplitude of soleus H-reflexes. The greatest reduction in soleus H-reflex amplitude appears at a C-T interval of 100-120 ms (Capaday et al. 1995; Iles 1996; Zehr and Stein 1999b). Inhibition of the soleus H-reflex is observed with no concomitant change in full-wave rectified and averaged EMG of the contracting soleus muscle (Capaday et al. 1995; Zehr and Stein 1999b).

### **Cutaneous reflexes**

Due to their polysynaptic pathways cutaneous reflexes are far more complex in their regulation than H-reflexes (reviewed in Brooke et al. 1997; and Zehr and Stein 1999a). Similar to H-reflexes, during locomotor tasks, cutaneous reflexes are modulated independently of background EMG amplitude (Brooke et al. 1997; Zehr et al. 2001b). Large amplitude reflexes can occur despite very low levels of background EMG and small reflexes with high levels of background EMG (Zehr and Chua 2000). The similar pattern of modulation of cutaneous reflexes in the arms and legs during rhythmic movements suggests similar control mechanisms (Zehr and Kido 2001; Zehr and Haridas 2003). This is probably due to central influences, from the brain or spinal cord (Zehr et al. 2001b).



### ***Interlimb coordination: possible pathways***

There is a debate as to which pathways mediate interlimb coordination. Interlimb coordination can be controlled in one of three ways: spinally, supraspinally, or an interaction between spinal and supraspinal pathways.

The reticulospinal tract could be involved since some of the descending fibres reach the lowest sacral segments (Nathan et al. 1996). However caudal to the cervical enlargement in humans, the majority of reticulospinal fibres are replaced by propriospinal neurons (Nathan et al. 1996). Apart from the reticulospinal tract the most likely candidates include corticospinal, spino-bulbo-spinal, and propriospinal pathways.

The lateral corticospinal tract projects to all segments of the spinal cord (Nathan et al. 1996). Although this tract is probably involved in interlimb coordination it is unlikely that short latency interlimb responses are transmitted through this pathway due to the early responses reported by several authors (Calancie et al. 1991, 1996, 2002; Meinck and Piesiur-Strehlow 1981; Piesiur-Strehlow and Meinck 1980; Zehr et al. 2001a). Using somatosensory evoked potentials and motor evoked potentials Nielsen et al. (1997) determined that the earliest possible latency for a transcortical pathway from the lower limbs in humans would be 70 milliseconds. The work by Calancie et al. (1991, 1996, 2002) on spinal cord injured subjects where the descending pathways were severely compromised, if not altogether absent, all but ruled out a cortical origin. The lateral corticospinal tract is probably involved in longer latency responses.

Another possibility is the spino-bulbo-spinal (SBS) pathway. This pathway relays sensory information to the bulbar reticular formation of the brain stem and projects to spinal motoneurons in several species including man (Shimamura et al. 1967; Shimamura 1973). In cats, this pathway has strong excitatory and inhibitory effects on flexor and extensor motoneurons, respectively, following cutaneous nerve stimulation (Shimamura et al. 1967; Shimamura and Aoki 1969). Lesion at the C1 level eliminates the SBS reflex and inhibition of extensor motoneurons is abolished (Shimamura et al. 1967). The SBS reflex is defined a long spinal reflex (>70 ms) and it is unlikely that the short



interlimb responses observed by several authors traverse the SBS pathway in humans. Similar to the corticospinal tract, the SBS pathway is likely to be involved in late responses and it might mediate changes of early responses in neurologically intact subjects. Baldissera et al. (2002) demonstrated that FCR H-reflexes undergo a stronger modulation during cyclical oscillations of the foot when conditioned with transcranial magnetic stimulation. Therefore descending drive can modulate early interlimb responses but it is improbable that short latency interlimb reflexes are of supraspinal origin.

There is evidence favoring a direct interlimb propriospinal pathway in humans. Several studies have demonstrated interlimb reflex responses considerably earlier than 70 ms in humans (Delwaide and Crenna 1984; Dietz et al. 2001; Gassel and Ott 1973; Kearney and Chan 1979; Meinck and Piesiur-Strehlow 1981; Piesiur-Strehlow and Meinck 1980; Zehr et al. 2001a). Zehr et al. (2001a) stimulated the superficial peroneal nerve and the superficial radial nerve and found similar latencies (~50 ms) in the responses of FCR and tibialis anterior, respectively, suggesting a spinal pathway of similar complexity. The strongest evidence of a propriospinal pathway comes from the work by Calancie and colleagues (1991, 1996, 2002). In these studies short latency interlimb responses were clearly demonstrated in subjects with spinal cord injuries. Unlike the SBS reflex, which is completely abolished by lesion at the C1 level, propriospinal reflexes are self-sufficient within the spinal cord (Shimamura 1973). Moreover, latencies (< 45 ms) in the upper limbs (forearm and hand) following tibial nerve stimulation all but rule out a supraspinal route for these short interlimb responses (Calancie et al. 2002).

Based on the available evidence it seems plausible that early interlimb responses are directly transmitted through a propriospinal pathway and that they interact with other pathways. However longer latency responses can be the result of several pathways including propriospinal, corticospinal, and spino-bulbo-spinal. Interlimb coordination likely involves several pathways acting in concert with each other.





### ***Functional implications of interlimb connections***

In the cat, the function of interlimb pathways coupling cervical and lumbar enlargements in the spinal cord has been ascribed to coordinating fore- and hindlimbs during locomotor activities (Miller and van der Meche 1976). In humans, locomotor tasks such as walking, running, and swimming also require the coordinated movement of our arms and legs. Previous studies have demonstrated that postural modifications (Delwaide et al. 1973, 1977) and movement (Hiraoka and Nagata 1999; Hiraoka 2001) of the arms may alter reflex excitability in the legs. Recent studies have shown that stimulating peripheral nerves in the arms changes the excitability of motoneuronal pools in the legs (Kagamihara et al. 2003; Zehr et al. 2001a). The present study is designed to investigate whether these interconnections between cervical and lumbosacral regions of the spinal cord in humans can modulate reflex excitability during movement. These pathways could be important in coordinating the arms and legs during movement.

### ***Interlimb coordination and central pattern generators: a coupling of CPGs?***

Human bipedal locomotion resembles a system consisting of two coupled oscillators (Viala and Vidal 1978; Wannier et al. 2001). In animals considerable evidence suggests that specialized neural circuits within the caudal spinal cord (central pattern generators or CPGs) control rhythmic movement of the hindlimbs, and similar circuits in the rostral segments coordinate locomotor activity of the forelimbs (Duysens and Van de Crommert 1998; Viala and Vidal 1978). This arrangement is thought to have been conserved in humans (Calancie et al. 1994; Dimitrijevic et al. 1998; Duysens and Van de Crommert 1998; Jackson et al. 1983b; Lamb and Yang 2000; Zehr and Haridas 2003). In humans, CPGs controlling rhythmic movement of the arms are thought to be located at the cervical level (Zehr and Chua 2000; Zehr and Kido 2001; Zehr et al. 2003) and at the lumbosacral level for the legs (Dimitrijevic et al. 1998). When compared to rhythmic activities of the lower limbs, recent studies demonstrate that reflexes in the upper limbs (cutaneous and H-reflexes) are similarly modulated during



rhythmic movements (Zehr and Kido 2001; Zehr et al. 2003; Zehr and Haridas 2003). CPGs in the cervical and lumbosacral cord may be coupled during locomotion to produce synchronous outputs for interlimb coordination and interlimb reflex modulation (Guadagnoli et al. 2000). Another possibility is that one CPG controls or “drives” the activity of the other CPG (Viala and Vidal 1978). Dietz et al. (2001) found that arm muscle responses to mechanical and electrical impulses applied to the leg, were stronger during normal gait than during walking with restricted arm swing and responses were almost absent during stance and sitting. These observations were also seen with similar levels of background EMG. This task-dependency suggests that interlimb pathways are gated by the activity of the CPGs during rhythmic movement such as normal gait (Dietz et al. 2001). Propriospinal neurons coupling the cervical and lumbosacral segments might be strongly inhibited and are disinhibited and/or facilitated during locomotion (i.e. turned on by the CPG) (Dietz 2002).

### ***Summary***

Reflexes in the legs exhibit both task and phase-dependent modulation during locomotor activities (Capaday and Stein 1986, 1987a; Simonsen and Dyhre-Poulsen 1999). The rhythmic movement of the arms during tasks such as walking and running could be partly responsible for the pattern of modulation of reflexes recorded in the leg. Pathways connecting regions of the spinal cord controlling the fore- and hindlimbs are present in several species and have been shown to influence the excitability of reflexes in both pairs of limbs (Miller et al. 1973). In humans the neural coupling of cervical and lumbosacral levels of the spinal cord has been demonstrated by stimulating peripheral nerves and recording responses in the arms and legs (Zehr et al. 2001a). However it remains unclear how movement influences these interlimb circuits in the spinal cord. The first objective is to test the hypothesis that movement of the arms can influence the amplitude of soleus H-reflexes. The few studies done so far did not address several key methodological issues, such as stimulus constancy and a consistent activation level of the target muscle. Since mechanisms of modulation were not



previously addressed the second objective is to test the hypothesis that changes in PSI are responsible for the modulation of soleus H-reflexes.

Coordination of the arms and legs could simply be an evolutionary remnant from a distant time where we used quadrupedal locomotion or it could be a neuronal mechanism conserved for its functional and efficient use. In either case understanding how these interlimb pathways are modulated during movement will add to our understanding of the control of movement in humans.





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## CHAPTER 2 – Paper

### Introduction

Typically, motor tasks such as walking, running, and swimming, demand that the upper limbs move rhythmically with the movement of the lower limbs. The movement of the arms during walking is due to muscular activity and is not simply a passive pendular movement (Jackson et al. 1983). Furthermore, when the upper limbs are restrained the arm musculature still contracts rhythmically (Fernandez-Ballesteros et al. 1965). Interlimb coordination is thought to stem from neural linkages connecting cervical and lumbosacral networks (Dietz 2002). Several recent papers have examined cutaneous and H-reflex modulation and have suggested that the neural control of rhythmic arm movement (Zehr & Kido 2001; Zehr et al. 2003; Zehr & Haridas 2003) is very similar to the control of rhythmic leg movement. It is thought that this control of reflex gain may rely on the output of central pattern generating (CPG) networks (Duysens and Van de Crommert 1998). To produce coordinated movement some form of linkage between the control of arm and leg movement would be anticipated. However, very little is known about the extent to which the interactions between the arms and legs can influence reflex excitability. Neural pathways linking the upper and lower limbs have been well established in other species and have recently been implicated for the control of human bipedal locomotion (reviewed in Dietz, 2002). To date these connections have been demonstrated in neurologically intact human subjects during static motor tasks by stimulating nerves in the arm and recording from muscles in the leg or vice-versa (Gassel and Ott 1973; Meinck and Piesiur-Strehlow 1981; Piesiur-Strehlow and Meinck 1980; Zehr et al. 2001). Calancie and colleagues (1991, 1996, 2002) reported similar responses in arm muscles in cervical spinal cord injured subjects following stimulation of mixed nerves in the leg.

Despite the important role for spinal pathways in coordinating movements of all four limbs in quadrupeds (Miller et al. 1973; Schomburg et al. 1978), little is known about interactions between arm movement and reflex excitability in the



legs of humans. A few studies have examined the effects of arm position on soleus H-reflex amplitude. Soleus H-reflexes in the right leg were facilitated when the right shoulder was in flexion (45-90° in front of the mid-axillary line) and inhibited when the left shoulder was positioned similarly (Delwaide et al. 1973, 1977; Eke-Okoro 1994). Passive movement of the elbow joint (flexion/extension) may facilitate (Hiraoka and Nagata 1999) while arm swing may inhibit soleus H-reflexes (Hiraoka 2001). However, these studies did not control several important factors such as stimulus constancy (M-wave size) and activation level of the soleus, and thus the results should be interpreted with caution.

The first objective of this study was to test the hypothesis that position and/or rhythmic movement of the arms alters reflex transmission in the soleus H-reflex pathway. It is generally accepted that presynaptic inhibition (PSI) is one of the major control mechanisms associated with rhythmic movement (for a review see Stein 1995) and is known to strongly modulate this reflex pathway (Brooke et al. 1997). The second objective was to test the hypothesis that changes in PSI were responsible for the modulation of soleus H-reflexes. Using conditioning stimuli known to decrease (cutaneous input from the sural nerve) or increase (Group I input from the antagonist muscle via common peroneal nerve) the PSI of the soleus H-reflex pathway was assessed. Some of these results were reported previously (Collins et al. 2002).

## **Methods**

### ***Subjects***

Ten subjects, ranging in age from 22 to 43 years, with no known history of neurological disorders, participated in this study. The subjects gave written consent to participate under the sanction of the Health Research Ethics Board at the University of Alberta. The experiments were conducted in accordance with the Declaration of Helsinki.



## ***Protocol***

The experimental set-up is illustrated in Figure 1. Subjects were seated in a chair with their backs supported. Hip, knee, and ankle angles were set at approximately 90°, 110°, and 90°, respectively. Both feet were placed securely on metallic blocks. Rhythmic arm cycling was performed in a clockwise direction at a comfortable pace (~60 rpm) using a custom-made hydraulic arm ergometer (described in Zehr et al. 2003) positioned directly in front of the subjects. Restraints were placed around the trunk, right thigh, and right foot to minimize unwanted movement. For each trial, subjects maintained a consistent low-level tonic contraction (~10% MVC) of their right soleus muscle using visual feedback of the filtered EMG signal.

Nerve stimulation (see below) was delivered during cycling at the 3 o'clock and 9 o'clock positions (described relative to the clock face) in separate trials. Subjects also performed static trials where they held their arms stationary at either 3 or 9 o'clock. The 3 o'clock position corresponds to the largest (most extended) elbow angle and maximal shoulder flexion (~70° in front of the mid-axillary line). In contrast, at the 9 o'clock position the elbow angle is smallest (most flexed) and the shoulder maximally extended (~10° behind the mid-axillary line).

## ***Nerve Stimulation***

All nerves were stimulated with bipolar surface electrodes using a Grass S88 (Grass Instruments, AstroMed Inc.) stimulator connected in series with SIU5 isolator and CCU1 constant current units. Stimulation was delivered approximately once every two to three cycles during cycling and pseudo-randomly between 1 and 3 s during static trials.

### **Soleus H-reflex:**

The tibial nerve was stimulated with single 1 ms square-wave pulses delivered over the right popliteal fossa. M-H recruitment curves were constructed at the start of each experiment to determine the maximal M-wave ( $M_{\max}$ ; mean of the three largest M-wave values), and to identify the stimulus intensity required to





obtain an H-reflex on the ascending limb of the curve with a small but stable M-wave. For the remainder of the experiment stimulation intensity was set to evoke an M-wave of this size ( $\sim 10\% M_{\max}$ ) on this part of the curve. M-wave amplitude was monitored online and stimulation intensity was adjusted occasionally to maintain consistent amplitude. Stimulation current was measured (mA-2000 Noncontact Milliammeter, Bell Technologies, Orlando, FL).

### **Sural nerve and Common peroneal nerve:**

The sural nerve was stimulated at the ankle just below the lateral malleolus with a train of 5 x 1 ms pulses delivered at 300 Hz at two times the radiating threshold. Radiating threshold was defined as a clear parasthesia radiating throughout the whole motoneuron territory of the nerve (Zehr et al. 1998). The interval between the sural nerve conditioning and the test H-reflex (C-T interval) was 80 ms.

The CP nerve was stimulated with single 1 ms square-wave pulses just distal to the head of the fibula at 1.5 times the motor threshold (Capaday and Stein 1995; Zehr and Stein 1999b). Motor threshold was defined as the weakest stimulation that produced a visible muscle twitch in tibialis anterior. The C-T interval was 100 ms.

During cycling and static trials reflexes were evoked by delivering nerve stimulation in three ways: 1) tibial nerve to evoke an H-reflex in soleus; 2) sural nerve + tibial nerve to reduce PSI of the H-reflex; 3) CP + tibial to increase PSI of the H-reflex. Additionally, to evaluate the postsynaptic effects of the conditioning stimulus on the soleus sural and CP nerve stimulations were delivered alone. Each type of nerve stimulation was delivered in a separate set of trials and the order of the trials was randomised across subjects.

### ***Electromyography***

Electromyography (EMG) was recorded with surface recording electrodes (Vermed incorporated, Bellows Falls, VT). EMG signals were pre-amplified and bandpass filtered at 30-3000 Hz (P511 Grass Instruments, AstroMed, Inc.). EMG



signals were full-waved rectified except for the ipsilateral soleus. The anterior deltoid (AD), soleus (SOL), tibialis anterior (TA) were recorded bilaterally. The vastus medialis (VM), biceps femoris (BF), biceps brachii (BB), and flexor carpi radialis (FCR) were recorded on the right side only. BF was only recorded in five subjects, BB and FCR in nine subjects.

### ***Data acquisition and analysis***

Data were sampled at 5000 Hz with a 12 bit A/D converter controlled by a custom-written computer LabView (National Instruments) program. For all trials 20 sweeps of data were collected. Sweep length was 300 ms with a 50 ms pre-stimulus window.

### ***EMG analysis***

#### **EMG activity during movement**

EMG activity from each muscle was recorded during all trials to determine the level of muscle activation during the different tasks and conditions. The prestimulus (50 ms) EMG was rectified and averaged and used as a measure of muscle activity at the time of nerve stimulation.

#### **H-reflexes**

Peak-to-peak amplitudes of M-waves and H-reflexes were determined off-line (custom-written software, Matlab, Nantick) from the single unrectified sweeps of ipsilateral soleus EMG. For each subject M-waves and H-reflexes were normalised to the corresponding  $M_{\max}$  to reduce inter-subject variability. Averages were calculated from all 20 sweeps in each condition for M-waves, H-reflexes, and prestimulus EMG in the right soleus.

#### **Responses evoked by sural and CP nerve stimulation**

Responses in soleus evoked by stimulating either the sural or CP nerve were quantified for each subject from subtracted EMG traces from the soleus by analysing for peak responses at early (50-80ms) and middle (80-120ms) latencies (see Zehr et al. 2001b). Responses were normalized to  $M_{\max}$  values obtained from the soleus.



## ***Statistics***

Using STATISTICA (StatSoft, Inc.) repeated measures analyses of variance tests (ANOVAs) were used to identify significant effects of movement, position, and conditioning on the amplitude of soleus H-reflexes, M-waves, pre-stimulus EMG levels, and responses evoked by sural and CP nerve stimulation. Planned comparisons were used to evaluate specific differences between conditions. Descriptive statistics are given as the mean  $\pm$  1 SE. An alpha level of 0.05 was used for statistical significance.

## **Results**

The experiments were designed to investigate the effect of arm cycling and position on the amplitude of soleus H-reflexes. The mean amplitudes of the unconditioned H-reflex during static trials at each position are used for the control values. The percentages below are expressed relative to the corresponding control values recorded at the 3 and 9 o'clock positions.

### ***Soleus H-reflexes during arm cycling***

The effect of arm cycling on the unconditioned soleus H-reflex is shown for a single subject (at 3 o'clock) in Figure 2. Despite similar M-waves and EMG level (not shown), H-reflex amplitude in this subject was reduced during arm cycling. For the group ( $n = 10$ ), soleus H-reflexes were significantly smaller (main effect for task:  $p = 0.0025$ ) during arm cycling compared to static controls. The bars in Figures 4 and 5 show the amplitudes of the unconditioned and conditioned H-reflexes (panel A), M-waves (panel B), and pre-stimulus background EMG (panel C) at the 3 and 9 o'clock positions, respectively. All data are expressed as a percent of the static unconditioned value (leftmost bars). Black and gray bars represent amplitudes during static positions and arm cycling, respectively. Asterisks (\*) indicate a significant difference between static and arm cycling and crosses (†) indicate significant difference compared to unconditioned static controls. On average, unconditioned soleus H-reflexes during arm cycling were 78.3% ( $p = 0.0005$ ; see Figure 4, panel A, leftmost bars)



and 91.2% ( $p = 0.0178$ ; see Figure 5, panel A, leftmost bars) of controls at 3 and 9 o'clock, respectively.

### ***Effects of conditioning the soleus H-reflex***

#### **Static trials**

The effects of conditioning stimuli on soleus H-reflexes with the upper limbs held stationary at 9 o'clock are shown for a single subject in Figure 3. Facilitation induced by sural nerve (dotted line) and inhibition (gray line) evoked by CP nerve stimulation can be seen. Averaged across all subjects, soleus H-reflexes conditioned with sural nerve stimulation were 112.3% at 3 o'clock and 114.5% at 9 o'clock. This effect was significant at 9 o'clock ( $p = 0.0069$ ; see Figure 5, panel A, middle bars) but not at 3 o'clock ( $p = 0.1143$ , see Figure 4, panel A, middle bars). CP conditioning significantly reduced the amplitude of soleus H-reflexes compared to control values across all tasks and positions. Reflexes were on average 70.3% at 3 ( $p = 0.0019$ ; see Figure 4, panel A, rightmost bars) and 84.3% at 9 ( $p = 0.0069$ ; see Figure 5, panel A, rightmost bars) o'clock relative to control amplitudes. The reduction was significant at 3 and at 9 o'clock.

#### **Arm Cycling**

During arm cycling, soleus H-reflexes with sural nerve conditioning were as a percentage of control values 80.4% at 3 o'clock and 101.4% at 9 o'clock. This reduction was significant at 3 o'clock ( $p = 0.0262$ ; see Figure 4 panel A, middle bars) but not at 9 o'clock ( $p = 0.5940$ ; see Figure 5, panel B, middle bars). For CP conditioning during arm cycling, H-reflexes were on average 61.2% and 75.2% of control values at 3 and 9 o'clock, respectively. This reduction was significant at 3 ( $p = 0.0007$ ; see Figure 4, panel A, rightmost bars) and at 9 ( $p = 0.0055$ ; see Figure 5, panel A, rightmost bars) o'clock positions.

### ***Effect of arm position on the amplitude of soleus H-reflexes***

To determine whether arm position influenced H-reflex amplitude, data recorded at the 3 and 9 o'clock positions were compared during static (see Figure





6, panel A) and arm cycling (see Figure 6, panel B) trials. There was no significant difference between H-reflexes evoked at 3 and 9 o'clock during static trials (main effect,  $p = 0.3442$ ). However, during arm cycling, H-reflexes evoked at 9 o'clock were significantly larger than those at 3 o'clock (main effect,  $p = 0.0091$ ). Mean amplitude was not significantly different for unconditioned ( $p = 0.4291$ ; see Figure 6, panel A, leftmost bars) and sural conditioned ( $p = 0.9313$ ; see Figure 6, panel A, middle bars) H-reflexes between the 3 and 9 o'clock position during static trials. However, H-reflexes conditioned with CP nerve stimulation during static trials were significantly larger at 9 compared to 3 o'clock ( $p = 0.0223$ ; see Figure 6, panel A, rightmost bars). Similarly during arm cycling the amplitude was not significantly different with unconditioned ( $p = 0.0567$ ; see Figure 6, panel B, leftmost bars) and sural conditioned ( $p = 0.0622$ ; see Figure 6, panel B, middle bars) H-reflexes. During arm cycling H-reflexes conditioned with CP nerve stimulation at 9 o'clock were larger than those at 3 o'clock ( $p = 0.0070$ ; see Figure 6, panel B, rightmost bars).

Thus only soleus H-reflexes conditioned with CP nerve stimulation showed a significant difference between the 3 and 9 o'clock positions (see Figure 6, panels A and B, rightmost bars).

### ***Responses to sural and CP nerve stimulation***

Across the group ( $n = 10$ ) stimulation of the sural nerve did evoke significant cutaneous reflexes at early and middle latencies (not shown) but these reflexes were not significantly affected by position or cycling of the arms. Similarly, significant early and middle latency responses (not shown), evoked by stimulating the CP nerve, were not significantly altered by position or cycling of the arms.

### ***EMG and M-wave amplitudes during H-reflex trials***

There were no significant differences ( $p > 0.05$ ) in pre-stimulus background EMG amplitudes for lower limb muscles (SOL, TA, BF, VM) between trials irrespective of conditioning or arm cycling. For all trials the



amplitude of M-waves and background pre-stimulus EMG of the soleus were not significantly different (see Figures 4 and 5, panels B and C). Arm cycling, however, resulted in significant differences in arm muscle EMG amplitudes ( $p < 0.05$ ). EMG activity of muscles of the ipsilateral limb (iAD, iBB, iFCR) were significantly higher when the ipsilateral arm was moving through the 9 o'clock position while EMG amplitude of contralateral AD was significantly higher when the ipsilateral was moving through the 3 o'clock position during arm cycling.

## Discussion

There are two main findings to this study. First, rhythmic cyclical movement of the upper limbs significantly reduces the amplitude of soleus H-reflexes, compared to stationary controls. Second, both the position and movement of the upper limbs influences somatosensory conditioning of the soleus H-reflex. This modulation arises prior to the motoneuronal membrane, probably by presynaptic inhibition of Ia afferent terminals.

### *Methodological considerations*

In the present study the amplitude of the direct motor response (M-wave) was used as indication of the constancy of the afferent test volley. By maintaining a similar sized M-wave for all comparisons it is assumed that the afferent volley also remains constant (Brooke et al. 1997; Dietz et al. 1990; Maeyer and Mawdsley 1965; Zehr et al. 2003). Further, H-reflex and M-wave amplitudes are typically normalized to  $M_{\max}$  to reduce inter-subject variability (Zehr 2002). However,  $M_{\max}$  can change over the course of an experiment (Crone et al. 1999) and at different limb positions (Gerilovsky et al. 1989). To minimize the impact of these effects in the present study the order of the different trials was randomized across subjects and the position of the ankle (thus soleus muscle length) was the same for all trials. Also, the activation level of the motoneuronal pool profoundly influences H-reflex amplitude (Capaday and Stein 1987). To ensure a consistent level of soleus motoneuronal activation in the current study, subjects maintained a similar plantar flexion contraction for all trials.



Heteronymous sources such as reciprocal inhibition from the antagonist (Baldissera et al. 1983; Cody and Plant 1989; Day et al. 1984) or recurrent inhibition from other leg muscles can affect H-reflex amplitude. However, there were no significant differences in EMG activity of leg muscles between tasks, thus it is improbable that the modulation was the result of heteronymous effects from leg muscles, at least arising from the muscles that we recorded (VM, BF, TA). Moreover, small and large H-reflexes are affected differently by excitatory and inhibitory conditioning signals, due to the involvement of different motor unit populations (Crone et al. 1990). However, Zehr et al. (2001a, 2003) showed that reflexes on three different parts of the M-H recruitment curves were modulated similarly during movement and thus in the present study H-reflexes were only sampled on the ascending limb of the M-H curve in each condition.

### ***Modulation of reflexes in leg muscles induced by arm movement***

There is some evidence that passive flexion/extension movement at the elbow joint (Hiraoka and Nagata 1999), rhythmic arm swinging (Hiraoka 2001) and static positioning (Delwaide et al. 1973, 1977; Eke-Okoro 1994) of the arms influences the amplitude of the human soleus H- and stretch reflexes. However due to several methodological concerns the source of the modulation is not clear. Hiraoka (2001) found that soleus H-reflexes were reduced (~10%) during arm swing but only when the shoulder was extended beyond the mid-axillary line; it was proposed that this modulation was due to lengthening of the anterior deltoid (AD) during the backward swing and the onset of the forward swing. With arm cycling, we also found a reduction (~9%) of H-reflexes during shoulder extension (i.e. 9 o'clock position) but H-reflexes were also significantly depressed (~22%) during shoulder flexion (i.e. 3 o'clock; see Figure 1 for arm positions). Therefore AD stretch alone cannot explain our findings since the reduction in H-reflex amplitude was also observed when AD was in a shortened position. In the present study although unconditioned soleus H-reflexes were significantly reduced at two positions during arm cycling compared to static controls (see figures 4 and 5; panel A) there was no significant difference in reflex amplitude between 3 and 9





o'clock during cycling or static trials. Previous studies (Delwaide et al. 1973, 1977; Eke-Okoro 1994) have shown that H- and stretch reflexes of the soleus are facilitated (~10%) during static shoulder flexion (i.e. arm in front 45°-90°) and inhibited (~7%) during static shoulder extension (i.e. arm behind 30°). We did not find an effect of arm position on unconditioned soleus H-reflex amplitude. This discrepancy from previous findings may be due to slightly different arm positions or lack of adequate controls in previous studies. Our results suggest that the reduction of soleus H-reflexes is the result of arm cycling (task-dependence) and not the position of the arm in the cycle (phase-dependence). We acknowledge, however, that we only sampled at two positions in the cycle and a phase-dependent effect may have been present if more positions were recorded. Furthermore since the H-reflex modulation occurred at similar levels of soleus EMG, we suggest that arm cycling acts via presynaptic inhibition (see below under Possible pathways).

### ***Interaction between arm movement and/or position and somatosensory conditioning***

The modulation of H-reflexes recorded at similar contraction levels is due predominantly to presynaptic inhibition (PSI) of the afferent volley (for reviews see Brooke et al. 1997; Meunier 1999; Rudomin and Schmidt 1999; Stein 1995; Zehr and Stein 1999a; Zehr 2002). One way to assess changes in PSI is to use methods to condition the H-reflex. Stimulation of the sural nerve at C-T intervals of 70-90 ms decreases PSI of the soleus H-reflex pathway (Demaire et al. 1989; Iles 1996) while CP nerve stimulation at C-T intervals of 100-120 ms increases PSI of this pathway (Capaday et al. 1995; Iles 1996; Zehr and Stein 1999). In the present experiments we tested whether arm movement or position influenced the effect of sural and CP conditioning (that is the segmental level of Ia PSI) on the soleus H-reflex. As anticipated, sural nerve stimulation facilitated the amplitude of the H-reflex during static trials (Delwaide and Crenna 1984; Demaire et al. 1989; Demaire and Ciancia 2000; Honore et al. 1983; Lebizet et al. 1983;). However, this sural nerve facilitation was significant at 9 but not at 3 o'clock (see



Figures 4 and 5, panel A, middle bars). During arm cycling H-reflexes conditioned by sural nerve stimulation were significantly reduced compared to static controls but only at 3 o'clock (see figure 4, panel A, middle bars). At 9 o'clock the PSI elicited by the arm cycling was reduced by the sural nerve stimulation (see figure 5, panel A, middle bars). These data suggest that both arm position and movement can gate the conditioning effect of the sural nerve onto the soleus H-reflex pathway.

CP nerve stimulation at 9 o'clock was the only instance where arm cycling did not further reduce the amplitude of H-reflexes (see Figure 5, panel A, rightmost bars). This is not due to a movement-induced saturation of PSI at 9 o'clock because during static and cycling trials H-reflexes evoked at 9 o'clock were significantly larger than at 3 o'clock (see Figure 6, panels A and B, rightmost bars). The most likely candidate is a gating of the conditioning stimulus at a spinal level. Capaday et al. (1995) demonstrated that the PSI of soleus H-reflexes induced by stimulating the CP nerve was modulated during the walking cycle. Our findings extend those of Capaday et al. (1995) to arm movements as well. Not only does arm cycling and position alter the PSI of the H-reflex but they also influence convergence from antagonist muscle nerves and cutaneous afferents on the PSI interneurons.

### ***Possible pathways of reflex modulation***

Several pathways could be responsible for the modulation of soleus H-reflexes during arm cycling. As illustrated in Figure 7, supraspinal and propriospinal inputs, arm position, and CPG activity may all be involved in modulating PSI of the afferent pathway to the soleus motoneuronal (MN) pool. The next sections will discuss the evidence for each of these.

Supraspinal and propriospinal pathways influence the excitability of the PSI pathway and the motoneuronal pool (see Figure 7, top panel, thick solid black lines). Studies using transcranial magnetic stimulation (TMS) and voluntary contraction of the homonymous muscle have shown that descending input from supraspinal centers can influence the PSI on this pathway during static



contractions (Iles and Roberts 1987; Iles 1996; Valls-Sole et al. 1994). The cancellation of the CP induced PSI of soleus H-reflexes by the Jendrassik maneuver is thought to be due to converging input from supraspinal centres and CP nerve on the same presynaptic pathway (Zehr and Stein 1999). Furthermore, soleus H-reflexes are facilitated by stimulating the ulnar nerve (Meinck and Piesiur-Strehlow 1981) and the median nerve (Kagamihara et al. 2003) at the elbow. Kagamihara et al. (2003) attributed this facilitation to reducing PSI through a long-loop pathway reaching levels at least as rostral as the pons. Along with supraspinal influences propriospinal pathways may also be involved. Based on short latency (< 45 ms) interlimb responses reported by several authors (Gassel and Ott 1973; Meinck and Piesiur-Strehlow 1980; Piesiur-Strehlow and Meinck 1981; Zehr et al. 2001) and the presence of interlimb responses in spinal cord injured subjects (Calancie et al. 1991, 1996, 2002) it is likely that propriospinal pathways coupling the cervical and lumbosacral enlargements of the spinal cord contribute to interlimb coordination. Interlimb reflex activity from 50 to 60 ms is likely confined to the spinal cord, while latencies of ~110 ms probably includes both spinal and supraspinal pathways (Calancie et al. 2002; Christensen et al. 2000). Propriospinal connections have been found in several species including man (Nathan et al. 1996) and direct coupling of the cervical and lumbosacral enlargements of the human spinal cord could convey afferent feedback from several upper limb muscles during arm movement.

Input from antagonist muscles (Capaday and Stein 1995; Iles and Roberts 1987; Iles 1996; Zehr and Stein 1999) and from cutaneous afferents of the leg (Demaire et al. 1989; Iles 1996) can alter the level of PSI at the Ia terminal to soleus motoneurons. Figure 7 shows the CP nerve with excitatory connections to the PSI interneuron and the sural (SU) nerve with inhibitory connections. Iles (1996) showed that activation of cutaneous afferents from the sural nerve reduced the PSI of soleus Ia afferents induced by stimulating the CP nerve suggesting convergence on a common presynaptic pathway. As mentioned previously the present study demonstrated that arm position and movement influenced somatosensory conditioning from sural and CP nerves. Joint, cutaneous and





muscle receptors from the arms (Figure 7, dotted box and lines) might send descending signal via supraspinal or propriospinal pathways on the presynaptic machinery of the lower limbs. The pattern of activation of several arm muscles during arm cycling is rhythmically modulated according to the position in the movement cycle (Zehr and Chua 2000; Zehr and Kido 2001; Zehr et al. 2003). Muscles that exhibit the largest modulation are the shoulder extensors (iAD, cAD), the elbow flexors (BB) and extensors (triceps) (Zehr and Kido 2001). In the present study, however, the reduction in soleus H-reflexes was observed at two positions in the cycle, where activation of arm muscles is markedly different, it is unlikely that activation of any one muscle is responsible for the modulation.

Perhaps a central pattern generator (CPG) activated during arm cycling is responsible for changing the PSI at the Ia afferent terminal (Figure 7, gray box and lines). Recent studies have shown that reflex modulation in the arms and legs is similar suggesting similar control mechanisms (Zehr and Kido 2001; Zehr et al. 2003, Zehr and Haridas 2003). The finding that the modulation is present during active, but not passive, movements suggests that CPG networks may be involved (Zehr et al. 2003). It is likely that CPGs at the cervical and lumbosacral level are coupled during locomotion and that they produce synchronous outputs for interlimb coordination and interlimb reflex modulation (Guadagnoli et al. 2000). Outflow from one or more CPGs could gate the activity of reflexes in the arms and legs during coordinated movements of both pairs of limbs.

Other possibilities include descending voluntary motor commands, anticipatory postural adjustments associated with planned movements or biomechanical factors, such as a weight shift affecting sensory input or sciatic transmission.

### ***Functional implications***

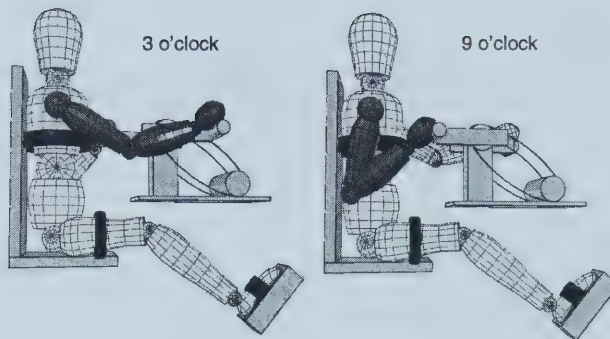
In the cat, the function of interlimb pathways coupling cervical and lumbar enlargements in the spinal cord has been ascribed to coordinating fore- and hindlimbs during locomotor activities (Miller and van der Meche 1976). In humans, locomotor tasks such as walking, running, and swimming also require





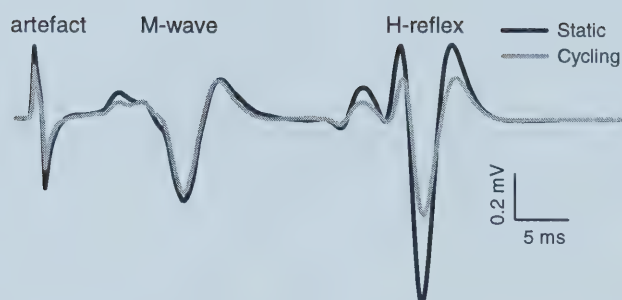
the coordinated movement of our arms and legs. It has recently been shown that stimulating peripheral nerves in the arms changes the excitability of motoneuronal pools in the legs (Kagamihara et al. 2003; Zehr et al. 2001) by activating interlimb pathways that couple cervical and lumbosacral regions of the spinal cords. The present demonstration that rhythmic arm cycling can change the gain of H-reflex pathways in the leg provides evidence that movement of the arms also activates interlimb pathways. Functional connections between cervical and lumbosacral regions of the spinal cord in humans are influenced by movement and that they might be involved in interlimb coordination.





**Figure 1.** Schematic representation of the experimental set-up showing subject's ipsilateral (shaded) arm at the 3 and 9 o'clock positions.

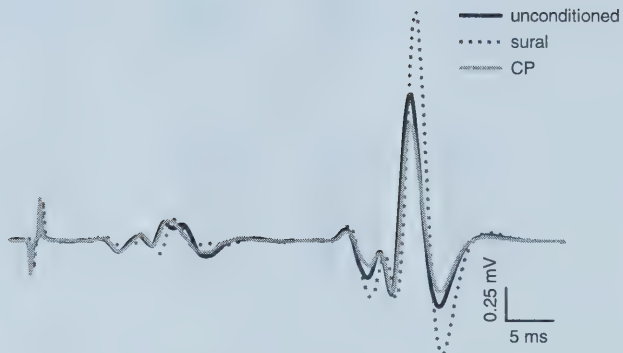




**Figure 2.** Reduction in soleus H-reflex amplitude with arm cycling in a single subject. Average of 20 sweeps during cycling (gray line) and during static trials (black line) recorded at the 3 o'clock position. Stimulus artefacts, M-waves, and H-reflexes are indicated.

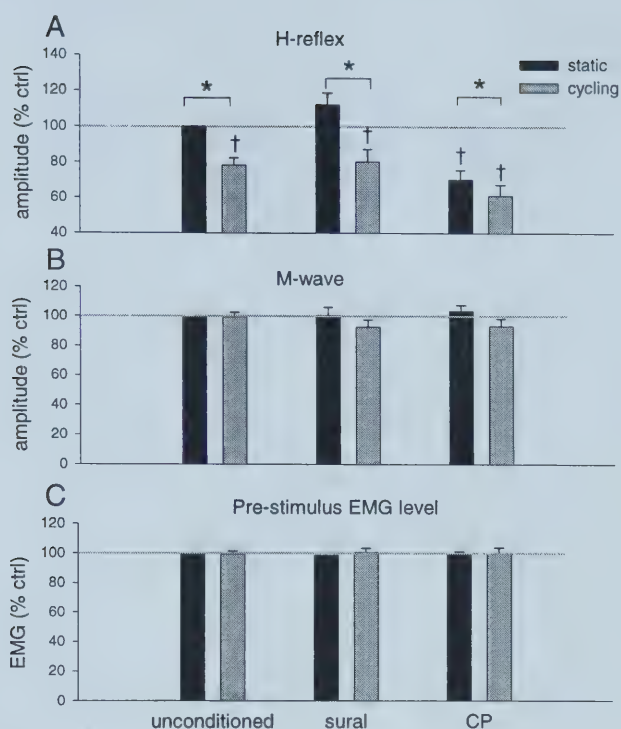






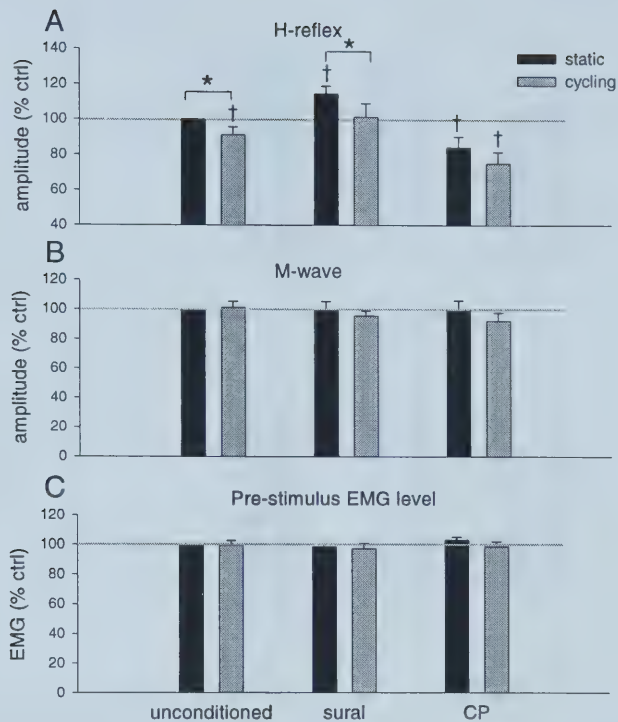
**Figure 3.** Effect of conditioning the soleus H-reflex with sural (dotted line) and CP (gray line) nerve stimulation during static trials recorded at the 9 o'clock position for a single subject compared to unconditioned control (black line). Lines are an average of 20 sweeps.





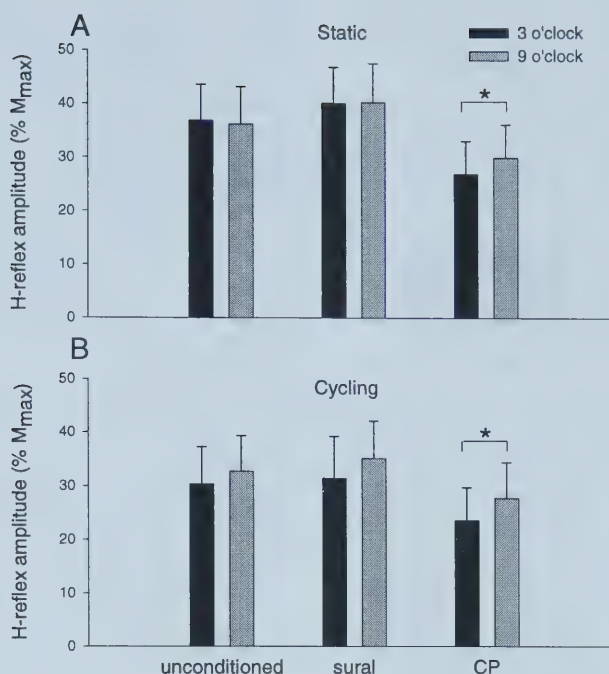
**Figure 4.** H-reflex (A), M-wave (B), and soleus EMG (C) data averaged across all subjects ( $n = 10$ ) recorded at the 3 o'clock position. Values are expressed as a percent of the control value (static, unconditioned at 3 o'clock). Asterisks (\*) indicate significant differences between static and cycling trials. Crosses (†) indicate significant differences compared to the control value. Shown are the mean  $\pm 1$  SE.





**Figure 5.** H-reflex (A), M-wave (B), and soleus EMG (C) data averaged across all subjects (n = 10) recorded at the 9 o'clock position. Values are expressed as a percent of the control value (static, unconditioned at 9 o'clock). Asterisks (\*) indicate significant differences between static and cycling trials. Crosses (†) indicate significant differences compared to the control value. Shown are the mean  $\pm$  1 SE.

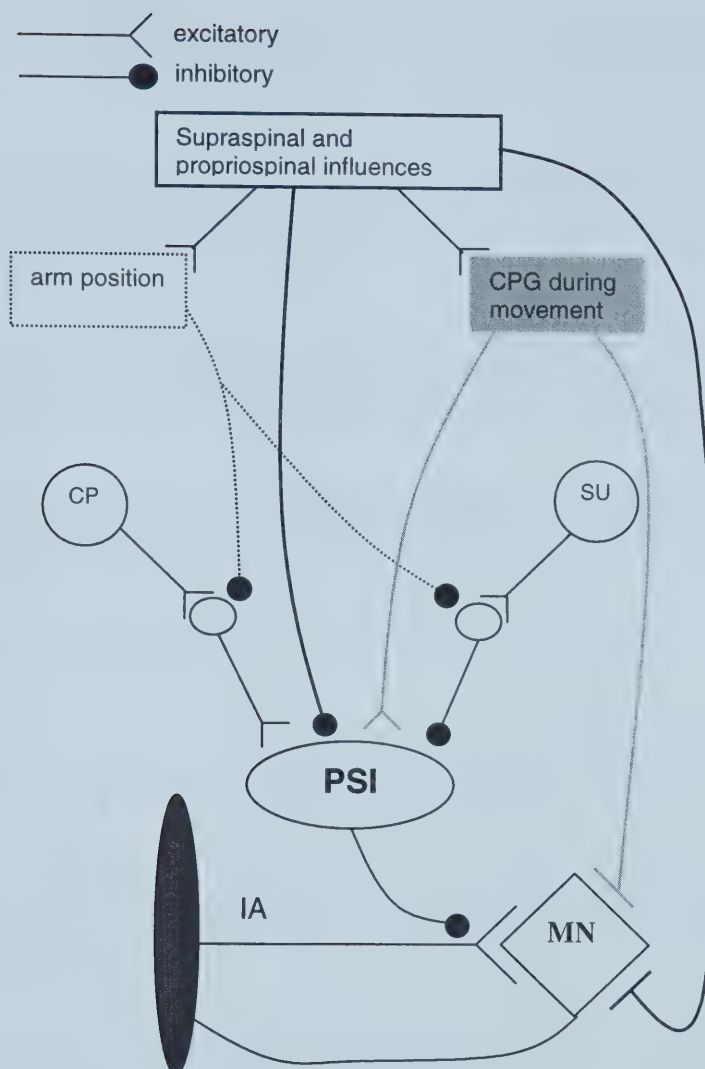




**Figure 6.** Effect of arm position on soleus H-reflex amplitude averaged across all subjects ( $n = 10$ ). Data was normalized to the maximal M-wave. There was a significant main effect of arm position during arm cycling but not during static trials. H-reflexes conditioned with CP nerve stimulation were significantly higher at 9 o'clock (gray bars) compared to 3 o'clock (black bars) during static and cycling trials. Shown are the mean  $\pm$  1 SE. Asterisks indicate significant differences between 3 and 9 o'clock.







**Figure 7.** Possible pathways that influence presynaptic pathways (PSI) and the soleus motoneuronal (MN) pool. Excitatory and inhibitory connections are shown with an open triangle and a filled black circle, respectively. At the bottom is a simplified H-reflex pathway from primary muscle spindles (Group IA) synapsing with alpha-motoneurons of the soleus. PSI changes the excitability of this pathway. PSI and the MN are controlled by supraspinal and propriospinal (thick black lines), and CPG pathways (gray lines). Input from the common peroneal (CP) and sural (SU) nerves have excitatory and inhibitory connections to PSI, respectively. CP and SU are influenced by arm position (dotted line).



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## CHAPTER 3 – Conclusion and general discussion

The purposes of this study were to investigate changes in reflex excitability in the lower limb during arm cycling and to determine if movement and/or position of the arms could influence conditioning volleys from two peripheral nerves onto the H-reflex pathway of the soleus in human subjects. We found that arm cycling significantly reduced the amplitude of unconditioned soleus H-reflexes at two different positions in the cycle but that position itself had no significant effect. However, it was also shown that conditioning volleys from the sural and CP nerve were influenced by position and by movement of the arms.

This is the first study to demonstrate an effect of arm cycling on reflex excitability in the leg and an effect of position and/or movement of the arms on somatosensory conditioning in the lower limb. This extends the findings by Hiraoka and Nagata (1999), in which passive movement at the elbow joint (flexion/extension) facilitated soleus H-reflexes and Hiraoka (2001) where soleus H-reflexes were inhibited by rhythmical arm swing. However due to several methodological considerations overlooked in the previous studies it was uncertain if the results were due to movement of the arms. Furthermore, previous studies have shown that placing the arm in front of the body (45°-90° in front of the mid-axillary line) facilitated lower limb extensor reflexes while having the arm placed 30° behind the mid-axillary line led to an inhibition (Delwaide et al. 1973, 1977; Eke-Okoro, 1994). Using two similar positions the present study found no evidence that position of the arms had a significant effect on the amplitude of unconditioned soleus H-reflexes. The fact that previous reports did not match activation level of the target muscle for every condition could explain why they found a significant effect of arm position. Activation level of the target muscle can have a profound effect on the amplitude of H-and stretch reflexes (Capaday and Stein, 1987b). To assess whether or not the modulation was due to changes in arm position or movement for every condition, subjects were asked to maintain a constant activation level of their soleus muscle. Assuming that the post-synaptic state of the muscle remained unchanged with a constant contraction (Stein, 1995) we were able to determine that presynaptic mechanisms were





responsible for the modulation. We presently used two different conditioning methods designed to decrease (sural nerve) or increase (common peroneal nerve) the level of presynaptic inhibition (PSI) at the Ia afferent terminal of the soleus. We found that position and movement of the arms significantly influenced the somatosensory conditioning volleys from sural and common peroneal nerves onto the soleus H-reflex pathway. Capaday et al. (1995) demonstrated that the conditioning volley from the common peroneal nerve onto the soleus H-reflex pathway changed during the walking cycle. The present study extends these findings to movement and position of the arms as well. Conditioning volleys designed to influence the excitability of the H-reflex pathway are dependent on the motor task and on the phase of the movement.

These results indicate that position and particularly movement of the upper limbs has strong influences on lumbosacral levels of the spinal cord. It is probable that rhythmical arm swing is partly responsible for the pattern of reflex modulation reported during human walking and running (Capaday and Stein 1986, 1987a; Simonsen and Dyhre-Poulsen 1999). However, it should be noted that reflex modulation in the lower limb might be influenced by various types of arm movement and not restricted to rhythmic movement. Postural adjustments of the arms and legs in various tasks probably allow for a coordinated response by modulating reflex excitability in both pairs of limbs simultaneously.

Although it is still unclear which pathways mediate these changes it is assumed that several pathways share a role including, but not exclusive to, reticulospinal, spino-bulbo-spinal, corticospinal, and propriospinal pathways. Propriospinal pathways are particularly attractive since previous studies have reported responses between the arms and legs with latencies too short to include a supraspinal route (Delwaide and Crenna 1984; Gassel and Ott 1973; Kearney and Chan 1979; Meinck and Piesiur-Strehlow 1981; Piesiur-Strehlow and Meinck 1980; Zehr et al. 2001). Furthermore, Calancie and colleagues (1991, 1996, 2002) reported responses in arm muscles following stimulation of peripheral nerves in the leg in spinal cord injured subjects where a supraspinal route is severely compromised if not altogether absent. This is strong evidence indicating



that propriospinal pathways mediate responses between the cervical and lumbosacral cord but their role in human interlimb coordination remains undetermined. It is probable that several pathways control interlimb coordination in humans and that they interact with each other.

In the cat, the function of interlimb pathways coupling cervical and lumbar enlargements in the spinal cord has been ascribed to coordinating fore- and hindlimbs during locomotor activities (Miller and van der Meche 1976). In humans, locomotor tasks such as walking, running, and swimming also require the coordinated movement of our arms and legs. It has recently been shown that stimulating peripheral nerves in the arms changes the excitability of motoneuronal pools in the legs (Kagamihara et al. 2003; Zehr et al. 2001) by activating interlimb pathways that couple cervical and lumbosacral regions of the spinal cord. By demonstrating that rhythmic arm cycling can change the gain of the H-reflex the current study provides evidence that movement of the arms also activates interlimb pathways. This indicates that interconnections between cervical and lumbosacral regions of the spinal cord in humans are influenced by movement and that they might be involved in interlimb coordination.

In conclusion, we have demonstrated that rhythmic cycling of the arms can influence the excitability of reflexes in the legs by activating interlimb pathways. Position and movement of the upper limbs also alters somatosensory conditioning volleys from flexor nerves and cutaneous afferents. It remains to be seen if similar effects are observed during more natural and unconstrained tasks.



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